REMARKS

Claims 1-3, 10, 13, 16, 19, 22[1], 25, 28 and 31-62 are pending; claims 31-62 have been withdrawn from consideration; 1-3, 10, 13, 16, 19, 22, 25 and 28 have been rejected.

Each of the claims has been amended to more clearly recite that which Applicant regards as the invention. The claims have also been amended to recite "alanine or an amino acid conservative for alanine" in place of the recitation that the amino acid at the position corresponding to position 118 of SEQ ID NO:1 is other than serine. Support for the recitation of alanine may be found in the specification in Example 8 (pages 86-87), where a mutant BAD polypeptide is described with the characteristics recited in claim 1, namely at least 95% homology to SEQ ID NO:1, an alanine in place of serine at position 118, and cell death promoting activity. Support for the recitation of an amino acid conservative for alanine would be understood to be inherent by the skilled artisan. Indeed, as discussed below, the Examiner explicitly recognized support for conservative amino acid substitutions in the outstanding Office Action.

Support for the recitation of "*in vitro*" cell death promoting activity in claim 1 may be found throughout the specification, for example in Example 8 (pages 86-87) discussed above, where a mutant BAD polypeptide as recited in claim 1 has cell death promoting activity *in vitro*.

No new matter has been added. Entry of the Amendment is respectfully requested.

---

[1] The Examiner appears to have mistakenly omitted claim 22 from the list of pending claims on the Office Action Summary sheet. The Examiner has, however, included it in the list of pending claims at page 2 of the Office Action, and in a number of the claim rejections.

I. Formal Matters

In the letter accompanying the present application, dated May 30, 2000, Applicant made a claim to benefit of U.S. Provisional Application No. 60/136,783, filed May 28, 1999. Applicant respectfully requests that the Examiner acknowledged Applicant's claim to domestic priority under 35 U.S.C. §119(e) to the provisional application.

II. Rejection of Claims Under 35 U.S.C. §112, Second Paragraph

At page 2 of the Office Action, claims 13, 25 and 28 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

1) The Examiner states that claim 13 is indefinite because while it recites the limitation "said domain," there is insufficient antecedent basis for this limitation in claims 1 and 10, from which claim 13 depends.

In response, Applicant includes herewith an amendment to claim 13, changing the word "said" to "a." In view of this amendment, claim 13 is now definite as written. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this portion of the rejection.

2) The Examiner states that claim 25 is indefinite because claim 25 is confusing. The Examiner explains that while claim 25 is drawn to a fragment of claim 1 comprising the amino acid sequence corresponding to positions 103-123 of SEQ ID NO:1, this fragment has a serine residue at position 118. However, the fragments recited in claim 1 do not have a serine at this position.

In response, Applicant includes herewith an amendment to claim 25, such that it now recites that the residue at position 118 of the fragment is not serine. In view of this amendment,

claim 25 is now definite as written. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this portion of the rejection.

3) The Examiner states that claim 28 is indefinite because while it recites the limitation "said naturally-occurring or wild-type mammalian BAD," there is insufficient antecedent basis for this limitation in claim 1, from which claim 28 depends.

In response, Applicants note that the present amendment directs the cancellation of claim 28, thus this rejection is moot. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this portion of the rejection.

III. Rejection of Claims Under 35 U.S.C. §112, First Paragraph

1) At page 3 of the Office Action, claims 1-3, 10-13, 19, 22 and 28 are rejected under 35 U.S.C. §112, first paragraph, as being non-enabled.

The Examiner states that the specification is enabling for a polypeptide or fragment thereof, wherein:

a) said polypeptide or fragment is at least 95% homologous to SEQ ID NO:1,

b) said polypeptide or fragment has an alanine at position 118 of SEQ ID NO:1, based on alignment with the BH3 domain of SEQ ID NO:1, and

c) said polypeptide or fragment has cell death promoting activity *in vitro*.

The Examiner does not find that the specification is enabling for a polypeptide or fragment thereof, wherein:

a) said polypeptide or fragment is at least 95% homologous to SEQ ID NO:1,

b) said polypeptide or fragment "does not have a serine" at position 118 of SEQ ID NO:1, based on alignment with the BH3 domain of SEQ ID NO:1, and

c) said polypeptide or fragment has cell death promoting activity *in vitro*.

At the bottom of page 6, the Examiner states that it is unpredictable that substitution of serine 118 of SEQ ID NO:1 with any amino acid, *which is not a conservative substitution*, would result in a mutant of BAD that has cell death promoting activity as claimed.

The Examiner further states at the top of page 7 that as the BH3 domain of BAD is necessary for binding and forming heterodimers with Bcl-2, one cannot predict that substitution of serine 118 of SEQ ID NO:1 with any amino acid, *which is not a conservative substitution*, would not distort the conformation of the BH3 domain, thereby preventing it from binding or forming a heterodimer with Bcl-2, which is necessary for cell death promoting activity of BAD.

In response, Applicant first notes that the Examiner refers to conservative substitutions of serine as being replacements that would be expected to result in a BAD mutant with cell death promoting activity. However, as Applicant has shown in Example 8 of the specification (pages 86-87), an alanine substitution results in a mutant BAD with full cell death promoting activity. Furthermore, alanine would not be considered to be a conservative substitution of serine (while serine is a neutral amino acid with a polar side chain, alanine is a neutral amino acid with a non-polar side chain; please see the enclose pages from the on-line version of the textbook *Molecular Biology of the Cell*, by Alberts et al., 3rd ed., panel 2-5 (1994)). Therefore, it is clear that non-conservative substitutions may be used to prepare a mutant BAD polypeptide that falls within the scope of claim 1.

However, to further prosecution of the application, Applicant includes herewith an amendment to the claims such that the phrase "does not have a serine at ...position 118" has been amended such that the claim now recites "an alanine or an amino acid conservative for alanine." There is clear support for the recitation of alanine, as the mutant BAD polypeptide

disclosed in Example 8 (pages 86-87) of the specification is identical to SEQ ID NO:1, with the exception that the serine at position 118 has been changed to an alanine. This mutant BAD is shown in the Example to have full cell death promoting activity.

The skilled artisan would inherently understand that the amino acids conservative for alanine would also result in a mutant BAD polypeptide with cell death promoting activity. As recognized by the Examiner, due to similarities in size and charge amino acids conservative for a particular amino acid are expected to have little effect on the activities and characteristics of the protein into which they are substituted. As further shown in the enclosed pages from a biology textbook, discussed above, the skilled artisan would readily understand which amino acids would be conservative substitutions for alanine.

In view of the amendments to the claims, and the points discussed above, Applicant asserts that the amended claims are fully enabled. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection.

2) At page 7 of the Office Action, claims 1-3, 10, 13, 16, 19, 22 and 28 are rejected under 35 U.S.C. §112, first paragraph, as being non-enabled.

The Examiner states that the specification is enabling for a polypeptide or fragment thereof, wherein:

a) said polypeptide or fragment is at least 95% homologous to SEQ ID NO:1,

b) said polypeptide or fragment has an alanine at position 118 of SEQ ID NO:1, based on alignment with the BH3 domain of SEQ ID NO:1, and

c) said polypeptide or fragment has cell death promoting activity *in vitro*.

The Examiner does not find that the specification is enabling for a polypeptide or fragment thereof, wherein:

a) said polypeptide or fragment is at least 95% homologous to SEQ ID NO:1,

b) said polypeptide or fragment "does not have a serine" at position 118 of SEQ ID NO:1, based on alignment with the BH3 domain of SEQ ID NO:1, and

c) said polypeptide or fragment has cell death promoting activity *in vivo*.

At page 9, the Examiner states that while substitution of serine 155 with alanine in murine BAD (SEQ ID NO:2) promotes cell death in HeLa cells transfected with BAD mutants, no disclosure is found in the specification concerning the promotion of cell death *in vivo* by the mutated BAD.

In response, Applicant respectfully notes that the pending claims are directed to mutant BAD polypeptides. The physical characteristics recited in the claims may be used to determine whether a particular polypeptide falls within the scope of the claims. Thus, the claims are directed to polypeptides alone, and not to methods of using the polypeptides. As the skilled artisan would clearly understand how to make and use the polypeptide recited in the claim based on the disclosure of the specification (SEQ ID NO:1 is provided in the Sequence Listing), Applicant asserts that the claims are fully enabled as written.

However, as the test for whether a particular protein falls within the scope of the claims may be solely performed *in vitro*, Applicant includes herewith an amendment to the claims such that the cell death promoting activity of polypeptides falling within the scope of the claims is determine through *in vitro* analysis.

In view of the points discussed above, Applicant asserts that the claims are fully enabled, and therefore Applicant respectfully requests reconsideration and withdrawal of this rejection.

IV. Rejection of Claims Under 35 U.S.C. §102

At page 12 of the Office Action, claim 25 is rejected as being anticipated by U.S. Patent No. 5,965,703 ("the '703 patent").

The Examiner states that claim 25 is drawn to a mutated isolated or synthetic polypeptide of BAD of claim 1, or a fragment thereof, wherein said polypeptide or fragment comprises the amino acid sequence corresponding to positions 103-123 of SEQ ID NO:1. The Examiner further states that the cited patent teaches the sequence of human BAD, which includes the sequence of positions 103-123 of SEQ ID NO:1. The Examiner thus concludes that the sequence recited in claim 25 is taught by the cited patent.

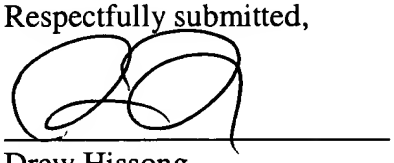
In response, Applicant again notes that claim 25 has been amended to affirmatively state that the residue corresponding to position 118 is not a serine residue. As the peptide sequence referenced by the Examiner includes a serine residue at position 118, the peptide sequence disclosed in the '703 patent does not anticipate the peptide sequence of claim 25. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection.

V. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



Drew Hissong
Registration No. 44,765

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE

23373
PATENT TRADEMARK OFFICE

Date: April 17, 2003